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1: Int J Pept Protein Res. 1994 Feb;43(2):127-38. Related Articles, Links

Pegylated peptides. II. Solid-phase synthesis of amino-, carboxy- and side-chain pegylated peptides.

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General procedures are presented for the site-specific pegylation of peptides at the NH2-terminus, side-chain positions (Lys or Asp/Glu) or COOH-terminus using solid-phase Fmoc/tBu methodologies. A model tridecapeptide fragment of interleukin-2, IL-2(44-56)-NH2, was chosen for this study since it possesses several trifunctional amino acids which serve as potential sites for pegylation. The pegylation reagents were designed to contain either Nle or Orn, which served as diagnostic amino acids for confirming the presence of 1 PEG unit per mole of peptide. NH2-Terminal pegylation was carried out by coupling PEG-CH2CO-Nle-OH to the free NH2-terminus of the peptide-resin. Side-chain pegylation of Lys or Asp was achieved by one of two pathways. Direct side-chain pegylation was accomplished by coupling with Fmoc-Lys(PEG-CH2CO-Nle)-OH or Fmoc-Asp(Nle-NH-CH2CH2-PEG)-OH, followed by solid-phase assemblage of the pegylated peptide-resin and TFA cleavage. Alternatively, allylic protective groups were introduced via Fmoc-Lys(Alloc)-OH or Fmoc-Asp (O-Allyl)-OH, and selectively removed by palladium-catalyzed deprotection after assemblage of the peptide-resin. Solid-phase pegylation of the side-chain of Lys or Asp was then carried out in the final stage with PEG-CH2CO-Nle-OH or H-Nle-NH-(CH2)2-PEG, respectively. COOH-Terminal pegylation was achieved through the initial attachment of Fmoc-Orn(PEG-CH2CO)-OH to the solid support, followed by solid-phase peptide synthesis using the Fmoc/tBu strategy. The pegylated peptides were purified by dialysis and preparative HPLC and were fully characterized by analytical HPLC, amino acid analysis, 1H-NMR spectroscopy and laser desorption mass spectrometry.

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